REMARKS

Claims 27-30 are currently pending in this application. New claims 43-52 have been added. Claims 21-26 and 31-42 have been canceled. Therefore, claims 27-30 and 43-52 are presented for examination.

New claims 43 and 51 are supported on page 7, lines 18-28 of the specification. New claims 44 and 52 are supported on page 10, lines 12-15 of the specification. New claims 45-50 are supported by the original claims and Example 5. These claims do not add new matter.

35 U.S.C. § 112, second paragraph

The Office maintained the rejection of claims 27-30 and claim 42 under 35 U.S.C. § 112, second paragraph, because it asserted that it is not clear what distinguishes the capture antibody from the revelation antibody. *See* Office Action of November 20, 2003, at 2. Applicants have amended claim 27 to recite "wherein the revelation antibody is conjugated to a label". Because the revelation antibody is conjugated to a label and the capture antibody is not, the two antibodies are distinguishable. Claim 27, and claims 28-30, which depend on claim 27, are now definite. Furthermore, Applicants have canceled claim 42, thus obviating the rejection of it. Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

New claims 43-52 are not subject to this rejection because these claims provide that the revelation antibody is produced in a different animal than is the capture antibody. Therefore, the revelation antibody can be distinguished from the capture antibody.

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35 U.S.C. § 103

The Office maintained the rejection of claims 27-30 under 35 U.S.C. § 103(a) as being obvious over alleged admissions in the specification about Falconar, in light of Zuk (U.S. Patent No. 4,2810,61) and Crooks (J. Gen. Virol., 1994). In response to Applicants' traversal of this rejection in the previous Amendment, the Office cited case law for the proposition that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Office Action of November 20, 2003, at 3.

Applicants respectfully disagree with this characterization of their previous response. As opposed to attacking the cited references individually, Applicants' argument was based on the proposition that "to establish *prima facie* obviousness of a claimed invention, all the claimed limitations must be taught or suggested by the prior art" M.P.E.P. §2143.03, and that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants discussed each cited reference individually to show that not all of the elements of independent claim 27, such as the antibodies preselected with the hexameric form of the NS1 protein, which demonstrate high affinity, were disclosed in the cited references. In contrast to the Office's characterization, each reference was not attacked individually but, instead, the claims as a whole were defended.

Applicants have amended claim 27 to indicate that the antibodies preselected against the hexameric form of the NS1 protein have a high affinity for the protein by including the following claim elements:

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(1) a polyclonal antibody with high affinity for the NS1 protein of the flavivirus in hexameric form, wherein the polyclonal antibody is preselected by immunocapture with the NS1 protein in hexameric form; and

(2) a mixture of purified anti-NS1 monoclonal antibodies with high affinity for the NS1 protein of the flavivirus in hexameric form, wherein the monoclonal antibodies are preselected by immunocapture with NS1 protein in hexameric form.

Antibodies with high affinity for the hexameric form of NS1 are supported on page 9, lines 12-26, of the specification. An antibody with "high affinity" for a protein is defined on page 9, lines 28-30, of the specification as one that has an affinity constant of less than 10^{-8} M. Furthermore, as described in Example 5(b) on pages 30-31, and in Figure 6, antibodies that are preselected against the hexameric form of NS1 can have affinity constants, such as 2.7×10^{-9} M and 3.10×10^{-9} M. Therefore, these antibodies have a "high affinity" for the hexameric form of the NS1 protein.

The use of antibodies that have a high affinity for the hexameric form of NS1 aids in differentiating the invention from the disclosure of Falconer, as Applicants indicated in their specification. Specifically, the specification notes that Falconar used a double-sandwich ELISA with antibodies directed against NS1 protein and that this assay "does not make it possible to detect the NS1 protein either in the case of primary infections in the acute or convalescent phase, or in secondary infections in the convalescent phase in which there is a high-titer of anti-NS1 antibodies . . . ." Specification at 6, line 26, through 7, line 6.

The inventors also noted in their specification that the method of Falconar has a sensitivity only to 4 ng/ml or 60 ng/ml. *See* Specification at 7, lines 3-6. In contrast, the assay of the claimed invention, using antibodies selected with the hexameric form of the

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NS1 protein, has a sensitivity of less than 1 ng/ml because of this high affinity. *See* Specification at 10, lines 12-15. In addition, while Falconar could not detect NS1 in primary infections of acute stage or convalescent stage infection, or in secondary infections when there is a high titer of anti-NS1 antibodies in the serum, *see* Specification at 7, lines 8-16, the invention is able to detect NS1 protein during these stages of infection, *see* Figures 3 and 5.

In fact, the Specification describes the unexpected results and advantages of including antibodies selected for the hexameric form of the NS1 protein in boxed sets on pages 9 through 10. Briefly, the specification teaches that it was surprising to learn that an antibody preselected with the hexameric form "makes it possible to significantly improve the sensitivity of the method and to detect the NS1 protein circulating in the blood of patients." Specification at 9, line 32 through 10, line 3. The Specification also indicates some of the advantages of using these antibodies include that the assay "may be carried out early, . . . is sensitive, . . . is rapid, . . . is relatively inexpensive, . . .[and] makes it possible to distinguish vaccinated individuals from individuals recently infected with a flavivirus." Specification at 10, lines 8-27.

Without disclosure of the claim element of antibodies that have high affinity and are preselected against the hexameric form of the NS1 protein, the Office cannot have presented a *prima facie* showing of obviousness. The antibodies that Crooks disclose are not shown to have been preselected with the hexameric form of NS1 or to have high affinity. Zuk does not disclose any antibodies to NS1 at all. Because these claim elements are not disclosed in any of the references, the Office has not made a *prima facie* case of obviousness, and Applicants request that this rejection be withdrawn.

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The Office also maintained the rejection of claim 38 under 35 U.S.C. § 103(a) in view of alleged admissions in the specification, Zuk, Crooks, and Harlow (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual, 1988). As discussed above, each and every element of the claimed invention has not been disclosed in the cited references and a *prima facie* case of obviousness has not been made. Zuk and Crooks do not disclose the element of high affinity antibodies that have been *preselected* with the hexameric form of the NS1 protein, and Harlow does not disclose any antibodies against NS1.

The Office presented new grounds of rejection of claims 27 and 41 under 35 U.S.C. § 103(a) in view of the alleged admissions in the specification, Zuk, Crooks, and Harlow. *See* Office Action of November 20, 2003, at 4. Specifically, the Office asserted that, in addition to the disclosure of Zuk and Crooks previously described, Harlow teaches that an antibody equivalent to the claimed "revelation antibody" can be labeled.

Applicants traverse this new rejection because, as stated above, no reference has been cited, which discloses the element of high affinity antibodies preselected with the hexameric form of the NS1 protein. Because this is an element of claims 27 and 41, Applicants respectfully request that the rejection be withdrawn.

Finally, the Office presented a new rejection of claims 27 and 42 under 35 U.S.C. § 103(a) in light of alleged admissions in the specification, Zuk, Crooks, and Tijssen (*in* Burdon, R.H. and vanKnippenberg, R.H., Laboratory Techniques in Biochemistry and Molecular Biology, 1985) *See* Office Action of November 20, 2003, at 5. The Office asserted that Tjissen teaches use of a labeled third antibody in immunoassays.

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For the same reasons as stated above, Applicants traverse this new rejection because no reference has been cited disclosing high affinity antibodies preselected by binding to the hexameric form of the NS1 protein. Without disclosure of each and every element of claims 27 and 42, the Office has not presented a *prima facie* case of obviousness, and Applicants request that the rejection be withdrawn.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 27-30 and 43-52 in condition for allowance. Applicants submit that the proposed amendments of claims 27-30 and new claims 43-52 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims previously examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, Applicants respectfully point out that the final action by the Examiner presented some new arguments as to the application of the art against Applicants' invention. It is respectfully submitted that entering of the Amendment would allow Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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Respectfully submitted,

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